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Frank C. Eisenschenk

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REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND UNDER 37 CFR 1.323
Docket No. BKR.106

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Pierre Monsan, Claude Bensoussan, Philippe Reulet, Renaud Nalin, Patrick Robe, Karine Tuphile, Benjamin Gillet, Pierre Pujic
Serial No.	:	10/591,087
Issued	:	December 7, 2010
Patent No.	:	7,846,874
Conf. No.	:	6343
For	:	Method for the Identification of a Metabolic Pathway Family by Means of Positive Selection

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND
UNDER 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears or should appear.

Patent Reads:	**Application Reads:**
Column 13, line 2:	Page 20, line 6:
"K. Struhi"	--K. Struhl--

Column 14, lines 63-64:	Page 23, lines 3-7:
"of {B} enabling growth is disrupted. **Step 7**: The passing by {B} into the metabolisation of {Ai}"	-of {B} enabling growth is disrupted. the mutated phenotype IV (Ai- ; B+)* of transposed clones capable of using {B} but not {Ai} in order to grow. The metabolic pathway in question enabling the conversion of the substrate {Ai} into the target product {B} is disrupted. **Step 7**: The passing by {B} into the metabolisation of {Ai}--
Column 22, line 6:	Examiner's Amendment in Notice of Allowability dated July 30, 2010 (original claim 19, renumbered as claim 1):
"comprises metabolic"	--comprises at least one metabolic--.
Column 22, lines 7-8	Examiner's Amendment in Notice of Allowability dated July 30, 2010 (original claim 19, renumbered as claim 1):
"of at least one substrate {Ai}"	--of substrate {Ai}--
Patent Reads:	**Application Should Read:**
Column 22, line 82:	Amendment Under 37 C.F.R. § 1.114 dated October 21, 2009 (original claim 19, step d), renumbered as claim 1):
"desired product [B}"	--desired product {B}--.

A true and correct copy of pages 20 and 23 of the specification and page 3 of the Examiner's Amendment accompanying the Notice of Allowability dated July 30, 2010 as filed which support Applicants' assertion of the errors on the part of the Patent Office accompany this Certificate of Correction.

Applicants' undersigned representative notes that the Examiner's Amendment amends line 15 and line 19 in step d) of original claim 19. Applicants believe that the Examiner would

have been using the most recently pending claims from the Amendment dated May 7, 2010 to make these amendments. However, Applicants note that the requested amendment by the Examiner to delete "at least one" is not present at lines 15 and 19 of original claim 19. Applicants note that an electronic communication was sent to the Examiner on July 15, 2010 with proposed amendments to the claims. and Applicants believe that the Examiner may have been referencing the line numbers from that communication when preparing the Examiner's Amendment as the phrase "at least one" appears on lines 15 and 19 which the Examiner intended to be deleted from original claim 19. In addition, Applicants note that it is believed to have been the Examiner's intention to delete the phrase "at least one" prior to "substrate {Ai}" shown at Column 22, line 7-8 for proper antecedent basis (see Column 22, line 2 wherein the phrase "containing substrate {Ai}" is indicated).

The fee of $100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

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Attachments: Copy of pages 20 and 23 of the specification
Copy of page 3 of Examiner's Amendment

line 9, step c), "at least one" has been deleted and replaced with ---said---.
After substrate {Ai}, ----selected from the group consisting of phytosterols, 1-phenyl-2-propanol and mandelonitrile---- has been inserted.

line 15, step d), "at least one" has been deleted.

line 19, "at least one" has been deleted.

Claim 25, line 7, step l), before library, ---metagenomic-- has been inserted.

Claim 32, line 2, before library, ---metagenomic--- has been inserted.

Claim 33, line 2, before library, ---metagenomic--- has been inserted.

Claims 21-24, 26-31 and 36 have been cancelled.

The cloning process, *i.e.* the introduction of the sequences of nucleic acid, preferably purified metagenomic DNAs, into the appropriate vector, requires numerous steps of molecular manipulation of the DNAs (in a non-limitative way for the restrictions, dephosphorylations, ligations, etc.) which have been widely described, for example in Current Protocols in Molecular Biology, Eds. F.M. Ausubel, R. Brent, R.E. Kingston, D.D. Moore, J.G. Seidman, J.A. Smith and K. Struhl, published by Greene Publishing Associates and Wiley Inter-Science. Two approaches for creating metagenomic libraries can be considered.

In a first preferred embodiment, the metagenomic library is formed directly in a **shuttle vector** specific of one or more hosts, preferably bacterial, for example as described in patents N° WO 01/40497A2 (Aventis Pharma, 1999) and W0 99/67374 (Biosearch Italia, 1999) for *Streptomyces*. In a second embodiment, the purified nucleic acids are cloned in a general vector, for example of the fosmid or BAC type, then the recombinant vectors are modified, individually or in a pool, advantageously by transposition as described in patent application N° PCT/EP 03/07765 (Libragen). In this process, the transposition makes it possible to introduce, either into the vector, or into the insert (disruption or activation), the genetic elements necessary for the transfer, the replication or the integration of the recombinant vector in the chosen host cell, preferably a bacterial host. This post-modification of the clones of the library can be implemented individually (metagenomic library structured in the format of 96 or 384 microplaques) or collectively (non-structured metagenomic library). The transformation of the population of host cells identified in step 1) by a population of cloned DNAs forms **Step 2** of this invention. In the two embodiments, the metagenomic library can be structured in advance in that all of the clones of the library are individualised in a format capable of being automated (96, 384, 1536 microplaques) or preferably be preserved in the form of a mixture of recombinant clones. In this preferred preservation mode, the library can advantageously be amplified in that the host cells, after transformation or infection, are multiplied over a specific number of cycles, leading to every recombinant clone of the library being represented by n copies in the amplified library, and the amplified library being able to be subjected to numerous simultaneous screening or selection tests, without any loss of diversity.

etc ; or (ii) the metabolic pathway of {Ai} passes via {B} and the metabolic pathway of {B} enabling growth is disrupted.

- the mutated phenotype IV (Ai- ; B+)* of transposed clones capable of using {B} but not {Ai} in order to grow. The metabolic pathway in question enabling the conversion of the substrate {Ai} into the target product {B} is disrupted.

Step 7 : The passing by {B} into the metabolisation of {Ai} is verified by evaluating the accumulation of {B} by techniques of analytical chemistry when a clone of phenotype (Ai- ; B-), isolated in step 4, develops on rich medium.

Step 8 : The genetic characterisation of the biocatalyst, *i.e.* characterisation of the gene or genes encoding the enzyme or enzymes involved in the conversion of {Ai} into {B}, is implemented by means of the transposed clones having the phenotype (Ai- B+). The genetic analysis of the nucleic sequences located on the disruption site or sites of the recombinant clones (Ai- ; B+) makes it possible to elucidate the genetic system(s) responsible for the conversion of {Ai} into {B}. The genetic analysis is implemented by any methods known by the man skilled in the art, including non-restrictively establishing sequences of nucleic acids, identifying coding and regulating sequences, etc.

This method makes it possible to gain access rapidly and directly (in a single step) to a metabolic pathway family capable of transforming a substrate {Ai} into a product {B}.

Alternative transformation-selection process

In an alternative embodiment of the invention, in particular when step 4 of the first embodiment does not make it possible to detect clones having a phenotype (Ai+ ; B+), any phenotypes (Ai- ; B+) offer the possibility of developing a receiving strain of phenotype (Ai- ; B+) capable of being co-transformed by a second metagenomic library (figure 4). This library can be the same as the first library or can be a distinct library. This alternative embodiment makes it possible to exploit, within the metagenomic library, the clones capable of converting at least one of the substrates {Ai} into target product {B} but incapable of metabolising {B} (clones not selected in step 4 of the first embodiment). This alternative embodiment involves several successive steps :

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,846,874

APPLICATION NO.: 10/591,087

DATED : December 7, 2010

INVENTORS : Pierre Monsan, Claude Bensoussan, Philippe Reulet, Renaud Nalin, Patrick Robe, Karine Tuphile, Benjamin Gillet, Pierre Pujic

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13,
Line 2, "K. Struhi" should read --K. Struhl--.

Column 14,
Lines 63-64, "of {B} enabling growth is disrupted.
Step 7 : The passing by {B} into the metabolisation of {Ai}"
should read --of {B} enabling growth is disrupted.
the mutated phenotype IV (Ai- ; B+)* of transposed clones capable of using {B} but not {Ai} in order to grow. The metabolic pathway in question enabling the conversion of the substrate {Ai} into the target product {B} is disrupted.
Step 7 : The passing by {B} into the metabolisation of {Ai}--.

Column 22,
Line 6, "comprises metabolic" should read --comprises at least one metabolic--.
Lines 7-8, "of at least one substrate {Ai}" should read --of substrate {Ai}--.
Line 82, "desired product [B]" should read --desired product {B}--.

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